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Studying the Overlap Between IBS and GERD: A Systematic Review of the Literature

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Abstract Evidence points to a significant overlap between irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD). In this study, we evaluate this overlap by conducting a systematic review of the literature. Six electronic databases from 1966 through January 2005 were screened by multiple search terms to identify all epidmiological evidence linking IBS and GERD. In addition, AGA meeting abstracts for 2003 and 2004 were also screened. All studies were validated by the authors and data extracted according to predefined criteria. As a separate search strategy, studies evaluating the prevalence of IBS and GERD in the general population were sought. These articles were obtained to compare the prevalence of IBS and GERD in the community to the degree of overlap. The search identified 997 original titles with 15 publications that fulfilled our eligibility criteria. Among the 15 studies, 7 determined the GERD maximum mean prevalence in patients already diagnosed with IBS to be 39.3% and the weighted mean 30.3%. The other 7 studies examined the prevalence of IBS in patients already diagnosed with GERD. The maximum mean prevalence of IBS in subjects with known GERD was 48.8% and the weighted mean 60.5%. Based on the prevalence of IBS (12.1%) and GERD (19.4%) in the community, the rate of IBS in the non-GERD community was calculated to be only 5.1%. There is a strong overlap between GERD and IBS that exceeds the individual presence of each condition. In the absence of GERD, IBS is relatively uncommon.

Keywords Irritable bowel syndrome · Gastroesophageal reflux disease · Functional bowel disease

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Introduction

Gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS) are two of the most prevalent gastrointestinal disorders. GERD, characterized by the symptoms of heartburn and acid regurgitation, is experienced by 7% of the population at least once a day and 44% at least once a month [1, 2]. IBS, characterized by the symptoms of abdominal pain/discomfort and disturbed defecation, is also very prevalent, with rates reported to be up to 20% in the general population [3].

Over the last 20 years, evidence is implying a strong overlap between GERD and IBS. For example, up to 30% of IBS patients complain of heartburn [4, 5]. From the opposite perspective, the prevalence of IBS in GERD patients is substantially higher than in the general population [6]. However, the problem with evaluating an overlap between these two conditions is that they are both so common that simple chance makes some overlap likely.

Although traditionally, IBS and GERD are considered separate entities, one common fact remains: their underlying pathogenesis remains unknown. In both conditions, some functional disturbance of motility can be observed, yet the cause of this change is enigmatic. In GERD, the commonly accepted functional disturbances are a reduction in resting lower esophageal sphincter (LES) pressure [7] and an increase in transient LES relaxation. In the case of IBS, alterations in transit [8–11] and small bowel motility [12,

13] are detectable. In one study, there appears to be common ground whereby resting LES pressure is abnormally low in IBS subjects compared to controls [14]. The latter study implies that the two conditions may have more in common than once appreciated. Adding to the complexity of understanding a relationship between IBS and GERD is the symptom heterogeneity even within IBS, whereby there are now defined subgroups including diarrhea-predominant (D-IBS) and constipation-predominant (C-IBS) IBS.

Accumulating evidence, as noted above, seems to point to a significantly higher mutual prevalence between IBS and GERD. If GERD is more common in IBS and IBS in GERD, and on a more speculative note, their conditions are somehow linked, then it would be important to know the prevalence of GERD or IBS without the other. In other words, what is the prevalence of IBS in a non-GERD population? In this study, we aimed to determine whether the overlap is truly excessive by conducting a systematic review of the literature and comparing this to studies of prevalence of GERD and IBS individually in the general population.

Methods

Systematic review for overlap of GERD and IBS

The goal of the systematic review was to determine the prevalence of IBS in GERD and GERD in IBS. To accomplish this, the following strategies were implemented.

First, an electronic search of six bibliographical databases was conducted: EMBASE (1980–present), Medline (1966–present), HEALTHSTAR (1975–2004), CINAHL (1982–present), Evidence-Based Medicine (1991–October 2004), Cochrane Library (fourth quarter 2004), Medscape (1998–present), and American Gastroenterological Association Digestive Disease Week (DDW) abstract CDs (2003 and 2004). The search terms used for IBS were "Irritable bowel syndrome," "functional diarrhea," "functional constipation," "spastic colon," and "IBS." These terms were combined with "gastroesophageal reflux," "GERD," "reflux," "dyspepsia," "non-ulcer dyspepsia," and "24-hour pH." This was done to search for articles which studied both conditions. Additionally, the PubMed "related articles" feature was applied for all studies meeting our entry criteria. The search outcome was then exposed to selection criteria that were predetermined at the study design phase. This search was conducted by two investigators (I.N. and E.M.) and at all levels by consensus between the two. The search was limited to the English literature and hand-searching of the literature was done.

The initial search yielded 997 unique titles. All titles were screened for relevancy to the original goal of investigation. Screening endpoints involved overlap of functional diseases, prevalence, and epidemiology. This step resulted in a total of 211 selected titles. For each title an abstract was then obtained. From the selected abstracts, those abstracts that studied an overlap between GERD and IBS were identified.

From abstract screening, 40 full papers were selected for superficial review. Each full text article was evaluated to determine eligibility. Eligibility criteria included randomized controlled, cross-sectional, or case-controlled studies examining the relationship between IBS and GERD and specifying the degree of overlap.

In the end, 26 full text articles were used for the in-depth analysis. During this in-depth analysis, 11 articles were related to nonulcer dyspepsia, without a specific assignment of GERD and IBS diagnosis with determination of overlap. This left 15 articles for systematic review. As part of this final review, the following data were collected: study type, publication year, perspective (whether GERD was initially studied for the prevalence of IBS, or vice versa), method of IBS and GERD diagnosis, and degree of overlap between IBS and GERD.

Systematic review of community prevalence of GERD and IBS

As a separate search strategy, studies evaluating the prevalence of solely IBS or solely GERD in the general population were sought. These were specifically not studies looking at overlap. Therefore, none of the 15 studies from the above systematic review were included in this collective.

Evaluating IBS and GERD prevalence exclusive of each other

Assuming that the systematic review was able to accurately represent the prevalence of GERD and IBS in the community and the overlap between the two conditions, a model was created to determine the prevalence of IBS in a community exclusive of GERD, and vice versa. The following formula was derived from the Law of Total Probability to determine the prevalence of IBS in the absence of GERD in the population:

$$= \frac{[(\text{rate of IBS in population}) - (\text{rate of GERD in population}) \times (\text{rate of IBS in GERD subjects})] \times 100}{1 - (\text{rate of GERD in population})}$$

For the determination of GERD in a non-IBS community a similar formula was used. In both scenarios, the model was used to generate an understanding of the impact of overlap

between these two conditions using the maximal mean prevalence. Since there was heterogeneity within some studies regarding the definition of GERD (i.e., some studies stated the prevalence of GERD based on prevalence of heartburn and also based on 24-hr pH), the larger of the two prevalence rates was used as the final value and included in the overall mean. A second mean was obtained using a weighted average since some studies had a small number of patients and others a very large one.

Results

We identified 26 publications (20 cross-sectional and 6 case-control studies) that met our eligibility criteria. Eleven publications were subsequently excluded because they focused on the overlap of IBS and nonulcer dyspepsia without specifically declaring GERD as the diagnosis.

Prevalence of GERD subjects with IBS

Of the remaining 15 studies, 8 examined the prevalence of GERD in patients already diagnosed with IBS [4, 5, 15–20]. Among these studies, the maximum mean prevalence of GERD in patients with IBS was 39.3% (Table 1). However, there was significant variability, with the prevalence ranging between 17% and 80%. Much of this difference appeared to depend on the method for diagnosing GERD in these IBS subjects (Table 2). Although more objective, higher rates of GERD were seen in IBS when pH or esophagitis (28%–80%) [16–18] on endoscopy was used as the diagnostic method to evaluate GERD, whereas the subjective symptom of nausea (as a presumed surrogate of GERD) was least related to IBS (17%) [4]. When a weighted average was used to adjust for sample size, GERD was present in 30.3% of IBS sufferers (Table 1).

Table 1 Prevalence of GERD in patients with irritable bowel syndrome

Authors [ref. no.]	Date of publication	IBS (*n*)	GERD prevalence (%)
Talley et al. [5]	2003	121	30.2
Hungin et al. [19]	2003	3880	21
Stanghellini et al. [18]	2002	146	28
Kennedy et al. [17]	1998	546	46.5
Jones et al. [20]	1992	350	79
Smart et al. [16]	1986	25	28–80
Whorwell et al. [4]	1986	100	17–30
Svedlund et al. [15]	1985	101	25
Maximum mean[a]			39.3
Weighted average			30.3

[a]Implies the mean of the highest prevalence rates in each study

Prevalence of IBS in subjects with GERD

The remaining seven studies examined the prevalence of IBS in patients already diagnosed with GERD [6, 21–26]. In these studies, the maximum mean prevalence of IBS in subjects with known GERD was 48.8% (Table 3). As in the study of GERD in IBS above, the prevalence of IBS in GERD was variable (31%–71%) and dependent on the methods used to diagnose IBS (Table 4) and GERD. When both Manning and Rome II criteria were applied to the same data set [23, 24], the Manning criteria identified a higher prevalence of IBS in the GERD subjects (Table 4). When a weighted average was used for these studies, IBS was seen to overlap in GERD at a rate of 60.5% (Table 3).

Prevalence of GERD and IBS in the general population

The systematic review identified 15 studies that described the prevalence of GERD in the community (Table 5) [1, 2, 27–39]. The average prevalence of GERD was 19.4% (2.7% to 40%) (Table 5) and the weighted average was 18.5%. Among studies, the range varied according to the criteria used to diagnose GERD. However, the overall prevalence rate of GERD in the community was lower than among IBS subjects as shown in Table 1 (Fig. 1).

During the same process, 7 studies were identified that evaluated the prevalence of IBS in the community (Table 6) [8, 40–45]. With respect to IBS, the average prevalence rate in the community was 12.1% (4.7% to 20.4%),

Table 2 Prevalence of GERD in IBS patients based on methodology of diagnosing GERD

Ref. no.	Esophagitis	pH positive	Reflux once a month	Reflux once a week	Reflux daily	Heartburn	Nausea
Talley et al. [5]						30.2	
Hungin et al. [19]						21	
Stanghellini et al. [18]	28						
Kennedy et al. [17]	46.5						
Jones et al. [20]						79	
Smart et al. [16]	80	50	56	52	28		
Whorwell et al. [4]						30	17
Svedlund et al. [15]						25	

Table 3 Prevalence of IBS in patients with gastroesophageal reflux disease

Author(s) [ref. no.]	Year of publication	GERD (*n*)	IBS prevalence (%)	Quality of GERD Dx
Wu et al. [23]	2004	107	37.4–47.6	24-hr pH
Wu et al. [24]	2004	172	36.7–45.9	24-hr pH
Chey et al. [22]	2004	80	31	Clinical
Bueno et al. [21]	2004	3318	64	Clinical
Raftopoulos [25]	2004	102	32.4	24-hr pH or esophagitis
Zimmerman [26]	2004	256	50	24-hr pH
Pimentel et al. [6]	2002	35	71	Clinical
Maximum mean[a]			48.8	
Weighted average			60.5	

[a]Implies the mean of the highest prevalence rates in each study

Table 4 The prevalence of IBS in gastroesophageal reflux disease based on the method of diagnosing IBS and IBS subtype

Ref. No.	Manning	Rome I	Rome II	D-IBS	A-IBS	C-IBS
Wu et al. [23]	47.6		37.4	35	52.5	12.5
Wu et al. [24]	45.9		36.7			
Chey et al. [22]	31					
Bueno et al. [21]			64			
Raftopoulos et al. [25]			32.4			
Zimmerman [26]		50				
Pimentel et al. [6]		71				

Table 5 Summary of studies of overall prevalence of GERD in the general population

Authors [ref. no.]	Year of publication	*n*	Prevalence (%)	Criterion
Talley et al. [27]	1985	327	22	Reflux
Mold et al. [28]	1991	313	14	Weekly heartburn
Ruth et al. [29]	1991	337	22	Reflux symptoms
Isolauri et al [1]	1995	1700	10.3	Daily heartburn
Locke et al. [30]	1997	2200	19.8	Heartburn weekly
Valle et al. [2]	1999	386	21	Heartburn monthly
Haque et al. [31]	2000	817	30	Reflux in past year
Kennedy et al. [32]	2000	3178	28.7	Heartburn in past year
Pan et al. [33]	2000	4992	5.77	24-hr pH and gastroscopy
Strobel et al. [34]	2001	1128	40	Reflux symptoms
Louis et al. [35]	2002	2000	28	Burning epigastrium in past year
Khoshbaten et al. [36]	2003	4207	2.7	Heartburn $\geq$ 3 episodes in 2 weeks
Wong et al. [37]	2003	2209	8.9	Weekly heartburn
Diaz-Rubio et al. [38]	2004	1780	9.8	GERD weekly
Camilleri et al. [39]	2005	9480	28	Heartburn/regurgitation
Maximum mean[a]			19.4	
Weighted mean			18.5	

[a]Implies the mean of the highest prevalence rates in each study

with a weighted average of 8.0%. This rate depended on the population studied as well as the criteria used to diagnose IBS. The prevalence of IBS in the general community was much lower than the prevalence of IBS in GERD subjects (Fig. 2).

The prevalence of GERD or IBS in the absence of the other

Based on the prevalence of IBS and GERD in the population and the degree to which there is overlap between the two conditions, the prevalence of IBS in a non-GERD population was determined from the average prevalence rates of each. In the same way, the prevalence of GERD in a non-IBS population was also calculated. From this we found that the prevalence of IBS in a non-GERD population was 5.1% (Fig. 2), which was much lower than that in the whole community population, 11.2% (Fig. 1). The prevalence of GERD in a non-IBS population was 16.6%.

In all studies there was significant heterogeneity concerning the method by which GERD was diagnosed (Tables 2, 3, and 5). The method of identifying IBS also varied between Rome and Manning Criteria (Tables 4 and 6).

Table 6 Summary of studies of overall prevalence of IBS in the general population

Authors [ref. no.]	Number of subjects	Year of publication	Prevalence (%)	Criteria
Dapoigny et al. [40]	20,000	2004	4.7	Rome II
Bommelaer et al. [41]	8,221	2004	12	Manning
Wilson et al. [42]	4,807	2004	10.5	Rome II
Gwee et al. [43]	2,276	2004	11	Manning
			10.4	Rome I
			8.6	Rome II
Saito et al. [3]	643	2000	20.4	Manning
			8.5	Rome
Caballero-Plasencia et al. [44]	264	1999	13.6	Manning
Agreus et al. [45]	1,290	1995	12.5	Manning
Maximum mean			12.1	
Weighted mean			8.0	

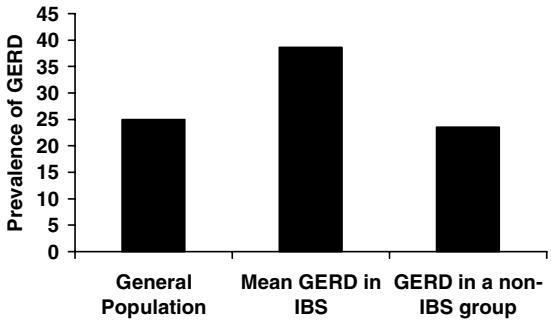

Fig. 1 Comparison of GERD prevalence in normal population, IBS subjects, and a calculated non-IBS group. Left: The prevalence of GERD in the general population based on the systematic review. Middle: The prevalence of GERD in patients with IBS shown as the mean value from the systematic review. Right: The prevalence of GERD estimated in a non-IBS population based on probabilities

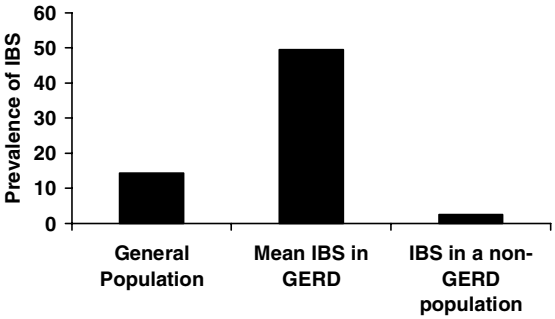

Fig. 2 Comparison of IBS prevalence in a normal population, GERD subjects, and a calculated non-GERD group. Left: The prevalence of IBS in the general population based on the systematic review. Middle: The prevalence of GERD in patients with IBS shown as the mean value from the systematic review. Right: The prevalence of IBS estimated in a non-GERD population based on probabilities

Discussion

IBS and GERD are two of the most common chronic gastrointestinal problems. As such, the expectation is that some GERD patients will suffer from IBS, and vice versa. Recent studies suggest that the overlap between IBS and GERD may be greater than anticipated by coincidence. In this systematic review, we show that there is a substantial overlap between IBS and GERD. The prevalence of GERD in IBS and of IBS in GERD is clearly higher than the average rate of each in the community. However, given this overlap, it may be more important to know the prevalence of each condition in the absence of the other. It appears that after eliminating GERD patients in the community, the prevalence of IBS in non-GERD subjects is low (5.1%). This is the first study summarizing this body of work with respect to IBS and GERD overlap.

In clinical practice, GERD is considered to be a unique entity caused by LES dysfunction and excess acid exposure in the esophagus. This then leads to heartburn as its main symptom. However, early studies found that only 50% of subjects with true GERD have heartburn as their main complaint [46]. While this study was based on tertiary care patients leading to referral bias of more atypical GERD, there is a subgroup of GERD patients whose primary complaint is not heartburn. Other symptoms of GERD that need to be factored in include, nausea, dyspepsia, dysphagia, and chest pain. With this concept in mind, pharmacologic agents designed to suppress acid are utilized and hence minimize symptoms [47]. In many cases, heartburn is relieved by such an approach, but functional symptoms such as nausea, regurgitation, pulmonary complaints, and, in many cases, bloating often do not resolve, possibly related to the fact that GERD is not caused by excessive gastric acid (but LES dysfunction).

In the case of IBS, treatment options are less than ideal due to our incomplete understanding of its pathophysiology. However, since a significant manifestation of IBS is bowel dysfunction, much of the attention in IBS is drawn toward the colon and rectum. Studies from the 1980s demonstrated that whole-gut transit is disturbed in IBS, such that slowing is seen in constipation-predominant IBS and acceleration is seen in diarrhea-predominant IBS [8]. In these studies, orocecal [noncolonic] transit was also altered in IBS [8], indicating alterations in small bowel transit. Recent attention in IBS is focused on abnormalities in the small bowel as well. These include disturbances of function [12, 13] and gas handling. Salvioli et al. recently demonstrated that infusion of gas into the colon of IBS patients was handled as appropriately as normal controls [48]. However, gas clearance from the jejunum of IBS patients was significantly impaired, with the result being reproduction of symptoms. The upper gut is least studied in IBS, but in one study of LES function, IBS patients had a lower resting sphincter pressure compared

to controls [7]. Taken together these data suggest that IBS may be a manifestation of a more widespread functional gut disturbance.

Recent efforts have been made to subcategorize functional bowel conditions for study purposes [49]. Although this has been very useful for reducing the heterogeneity of patients in clinical protocols, it has to some degree de-emphasized the similarities among functional disorders. This study demonstrates a significant overlap between IBS and GERD. This, taken with data showing that IBS patients have a lower LES resting pressure, begins to suggest that IBS and GERD may be related by more than chance. It also calls attention to the fact that although acid suppression helps in GERD, the pathogenesis of low LES resting pressure is as unknown as the cause of IBS. Perhaps a common pathophysiologic mechanism is responsible for both IBS and GERD.

An even more striking finding in this systematic review is shown in Fig. 2. Based on these data, it seems that few patients have IBS without coexisting GERD. These data might excite a belief that IBS is a subset of GERD. However, this systematic review is not designed to prove this concept. The finding is intriguing and highlights a need for further population studies to establish the prevalence of each condition without the other to answer this question more accurately.

Another important message from these data is that the upper gastrointestinal tract problems can be among the constellation of abnormalities in IBS. It is clear that dysfunction of the bowel in IBS is not limited to the colon. Visceral hyperalgesia, particularly rectal hyperalgesia, has long been associated with IBS [50]. Esophageal hyperalgesia is also seen in IBS [51]. If this is the case, then perhaps IBS subjects do not have pathologic reflux; rather they are more sensitive to physiologic reflux. The data in this systematic review, while not dismissing the issue of hypersensitivity, demonstrate that IBS patients not only have low LES resting pressure [7] but also true pathologic reflux [16] based on pH testing in 50% of cases. Conversely, IBS is very common in patients with true GERD based on abnormal pH testing [6]. This observation detracts from the simple argument that esophageal symptoms in patients with IBS arise from visceral hypersensitivity.

An important issue that needs to be at least discussed is nonerosive reflux disease (NERD), whereby symptoms characteristic of GERD such as heartburn are observed in patients in whom no endoscopic evidence of acid induced injury is seen on endoscopy [52]. It seems possible that NERD too may be associated with IBS, but in this systematic review the studies demonstrating overlap between the two conditions did not allow for the determination of NERD.

While the data are very enlightening regarding the relationship between IBS and GERD, the systematic review poses some problems. First, the techniques for diagnosing IBS and GERD were somewhat heterogeneous. In the case of IBS, although the methodologies were different, the rates were quite similar between techniques. However, in the case of GERD, the diagnostic criteria were more heterogeneous, with techniques of determining GERD ranging from nausea to endoscopic esophagitis. In the case of studies defining GERD based on endoscopic esophagitis [16–18], these studies were based in tertiary care centers and in smaller groups of patients due to costs. Although more accurate, in determining true GERD, referral bias and small sample size likely account for a wide range of overlap (28%–80%). Although one might argue that larger, more community-based studies of overlap would be more reflective of the true overlap in the general population between IBS and GERD, these studies too have problems. In these large-scale community studies, the basis of diagnosing GERD and IBS is symptom self-reporting without confirmatory tests or physician validation, calling the diagnostic accuracy into question. For this reason we have represented the mean overlap in both an absolute mean method (ignoring the size of study) and a weighted average to adjust for small studies with tertiary referral bias and represent larger studies as well.

In summary, this systematic review demonstrates that IBS and GERD appear to overlap to a degree that is greater than their individual prevalence in the community. Furthermore, the data show that each condition is less prevalent in the community if the other is excluded from analysis. This suggests a possible causal relationship. The data also draw attention to the fact that proximal gastrointestinal disturbances are also common in IBS and that IBS is not isolated colon dysfunction. While the pathogenesis of both IBS and GERD remains unknown, this study suggests that evaluating the similarities between IBS and GERD may be more important than subgrouping functional disorders as we get closer to understanding the true pathophysiology of these conditions.

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